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REGULATORY STABILITY CONSIDERATIONS FOR BIOLOGICAL PRODUCTS

By Lotte McNamara, Ph.D.
Managing Director, BioProcess Technology Group

INTRODUCTION

Stability studies are considered an essential element of product development. Stability studies are typically conducted under long-term storage, accelerated and stressed conditions to determine product shelf life. Stability study results are also used to support evaluation of shipping and handling excursions. During research and early preclinical development of biological products, the molecule is typically frozen in a simple isotonic buffer to maintain stability. Once proof-of-concept (**in vitro** and **in vivo** studies) has been established, formulation development studies are initiated to attain a formulation that is suitable for use in humans. The selected formulation should afford adequate stability during product storage, distribution and administration in the clinic. Typically, it is preferred to store biological drug substance frozen and biological drug product at refrigerated or room temperatures.

The IND-enabling stability studies should be conducted using material considered representative of that produced by the clinical manufacturing process. Stability data should be available at the time of submission of an initial application to initiate first-in-human (FIH) clinical trials.

Stability studies supporting a marketing application should be designed according to guidance provided by the International Committee for Harmonization (ICH), in order to support the marketing application. ICH Q1A(R2)[1] and ICH Q5C[2] both describes studies required to support registration dossiers to confirm product stability during the intended storage period. While ICH Q1A(R2) describes the design of stability studies for new molecular entities, ICH Q5C takes into consideration the special circumstances that may be considered for storage of biological products and should therefore be used to design stability studies for biologics. The ICH guidance does not specifically address stability studies to support clinical trials. While most companies align their stability strategies during clinical development with the ICH guidance, stability studies intended to support FIH clinical trial applications are not required to and cannot always be designed in accordance with the ICH guidance for testing time points and storage conditions. This is due to material and timing limitations at this early stage of development.

Region-specific regulatory guidelines exist that describe the general content expectations for clinical trial applications. However, no specific regulatory requirements are published by the FDA or the EMA regarding how much stability data is necessary to include in an initial clinical trial application for a biologic product.

As companies are often working against compressed timelines to initiate clinical trials as early as possible, they likely have only just released their first clinical trial batch prior to submitting the clinical trial application. None or only very limited stability data exists for the Good Manufacturing Practice (GMP) batch intended for use in the clinical trial studies. The only available stability data supporting the clinical trial application is therefore derived from early non-GMP batches. Setting a proposed shelf life for the clinical trial material can thus be challenging.

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[1] ICH Q1A(R2): ICH Harmonised Tripartite Guideline: Stability Testing of New Drug Substances and Products. 06 Feb 2003.

[2] ICH Q5C: ICH Harmonised Tripartite Guideline. Stability: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. 30 Nov 1995.

REGULATORY REQUIREMENTS FOR STABILITY INFORMATION ACCOMPANYING CLINICAL TRIAL APPLICATIONS

The US Code of Federal Regulations 21 CFR 312[3] provides the statutory regulations for investigational drug products governed by the FDA. These regulations do not provide specific requirements for the amount of drug substance and drug product stability data necessary for submission of an investigational new drug (IND) but emphasizes the step-wise nature of product development and availability of data. The FDA guidance from 1995[4] concerning information to be submitted in an IND for Phase 1 clinical studies outlines the following requirements for stability data: ***"A brief description of the stability study and the test methods used to monitor the stability of the drug product packaged in the proposed container/closure system [..and drug substance stored in container/closure systems representative of the proposed bulk storage container/closure system..] and storage conditions should be submitted. Preliminary tabular data based on representative material may be submitted. Neither detailed stability data nor the stability protocol should be submitted."*** While the guidance for Phase 1 clinical studies indicates very limited stability study information is required, the FDA guidance from 2003[5] concerning INDs for phase 2 and 3, recommends additional information to be submitted: ***"A description of the stability program to support the drug product [..and drug substance..] under clinical investigation in phase 2 should be submitted. [..] Stability data from representative clinical trial materials used in phase 2 should be provided in annual reports as the data become available."*** Finally, the GMP guidance from 2008[6] supports the phase-appropriate approach to GMP during product development and states: ***"We recommend initiation of a stability study using representative samples of the phase 1 investigational drug to monitor the stability and quality of the phase 1 investigational drug during the clinical trial (i.e., date of manufacture through date of last administration)."***

Regulation No 536/2014[7] provides the legislation related to investigational medicinal products in the European Union. The EMA guideline[8] on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials states that ***"A stability protocol covering the proposed storage period of the product should be provided, including specification, analytical methods and test intervals. […] The quality of the batches of the product placed into the stability program should be representative of the quality of the material to be used in the planned clinical trial. […] Stability data should be presented for at least one batch made by a process representative of that used to manufacture material for use in the clinical trial. In addition, supportive stability data on relevant development batches or batches manufactured using previous manufacturing processes should be provided, if available. […] Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the product during the different phases of clinical development."***

In summary, stability studies are expected for a clinical trial application, but there is no defined guidance on the amount of stability data and which batches should be selected to conduct the studies. It is noteworthy, however, that regardless of the stability study design and availability of data, it is expected that the studies be conducted using material representative of the clinical trial material and that the material is stored in container closure systems representative of those to be used for storing clinical trial product.

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[3] Title 21--Food and Drugs Chapter I--Food and Drug Administration. Department of Health and Human Services. Subchapter D - Drugs for Human Use. Part 312: Investigational New Drug Application.

[4] FDA Guidance for Industry. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products. November 1995.

[5] FDA Guidance for Industry. INDs for Phase 2 and Phase 3 Studies. Chemistry, Manufacturing, and Controls Information. May 2003.

[6] FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs. July 2008.

[7] Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/E. Official Journal of the European Union. L 158/1. 27 May 2014.

[8] EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. EMA/CHMP/BWP/534898/2008 Rev. 2. 27 Jan 2022.

EXPIRY DATE FOR CLINICAL TRIAL MATERIAL

The stability of clinical trial material must be demonstrated during the conduct of clinical trials in both the United States and in the European Union. Specifically, for clinical trials conducted in the European Union, the drug product label must include an expiry date per Regulation (EU) No 536/2014[7], Annex VI for Labelling of Investigational Medicinal Products and Auxiliary Medicinal Products, Section A1.1: ***"The following particulars shall appear on the immediate and the outer packaging […] k) period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity")***. Conversely, drug product labels for trials conducted in the United States do not include expiry dates. Hence, companies may delay submission of clinical trial application in the European Union to ensure sufficient stability data is available to support an expiry date that allows use of the clinical material for an extended time period following trial initiation.

The expiry date is determined as described in the EMA guideline[8] for quality documentation concerning biological investigational medicinal products in clinical trials: ***"The requested storage period should be based on long term, real time and real temperature stability studies, as described in ICH Q5C. However, extension of the shelf-life beyond the period covered by real-time stability data may be acceptable, if supported by relevant data, including accelerated stability studies and/or relevant stability data generated with representative material. The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by real time stability data obtained with representative batch(es). However, extension of the shelf life beyond the intended duration of the long-term stability studies is not acceptable."***

The shelf life may then be extended as additional data becomes available by submission of non-substantial amendments, assuming a stability protocol was submitted with the initial investigational medicinal product dossier (IMPD). The submitted stability protocol must include a final testing time point that corresponds to the final, targeted expiry date. Additionally, a commitment must be made to inform the authorities of any unexpected results (e.g., out-of-specification) that are obtained during testing at the long-term storage condition.

Extrapolation of the available stability data using linear regression for biologics can be performed to provide some estimation of anticipated shelf life. However, the statistical approach described in ICH Q1E to test batch data for poolability and support extrapolation to extend a retest date or shelf life is not recognized as suitable for use to support extrapolation of shelf life for biological products.

[7] Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/E. Official Journal of the European Union. L 158/1. 27 May 2014.

[8] EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. EMA/CHMP/BWP/534898/2008 Rev. 2. 27 Jan 2022.

IN-USE STABILITY STUDIES FOR DRUG PRODUCT

Prior to entering clinical trials, it is also important to perform stability studies under in-use conditions for the drug product. These typically include studies to evaluate product physicochemical stability during the in-use period following reconstitution and/or dilution. The stability-indicating analytical methods employed in the studies must be demonstrated to be suitable for use for analysis of diluted product samples. This may require development and phase-appropriate validation of methods that can measure product at much lower concentrations and in different matrices than that for the formulated, non-diluted drug product.

Additionally, per ICH Q8(R2)[10]: ***"Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented in this section."*** More recently, additional scrutiny has been applied by the agencies regarding in-use stability study data submitted in IND applications and IMPDs. For any product that is stored for more than four hours at room temperature or more than 24 hours at refrigerated conditions after breach of the original container closure configuration (e.g., reconstituted or diluted), microbial challenge studies are typically required. The EMA guideline[8] states that: ***"In-use stability data should be presented for preparations intended for use after reconstitution, dilution, mixing or for multidose presentations. These studies are not required if the preparation is to be used immediately after opening or reconstitution."***

A more recent FDA draft guideline issued for IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases[11] provides a good description of the general expectations for microbial challenge studies. Recommended study conditions and microbial strain selection are summarized in this guidance.

[8] EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. EMA/CHMP/BWP/534898/2008 Rev. 2. 27 Jan 2022.

[10] ICH Q8(R2): ICH Harmonised Tripartite Guideline. Pharmaceutical Development. August 2009.

[11] FDA draft guidance. December 2021. **IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Chemistry, Manufacturing, and Controls Recommendations Guidance for Sponsor-Investigators.**

STABILITY-INDICATING ANALYTICAL METHODS

Process-related impurities do not increase during storage and are therefore not considered relevant attributes to monitor during stability studies. Rather, the stability studies focus on monitoring product-related impurities. To ensure the appropriate analytical methodologies are applied to the stability program, the stability-indicating properties of the analytical methodologies must be documented through analysis of stressed samples. Further, the analytical methodologies must be validated in a phase-appropriate manner prior to use in the stability program supporting evaluation of the clinical trial material.

ICH Q14[12] and USP<1220>[13] Analytical Procedure Life Cycle describes the expectations of analytical procedure life cycle. For early-stage development the analytical procedures are expected to be suitable for use and are typically evaluated for accuracy, precision, linearity, range, LOD, and LOQ, as suitable depending on the analytical methodology. In addition, some robustness studies may be performed.

[12] ICH Q14. ICH Harmonised Guideline. Analytical Procedure Development (Draft version). 24 March 2022.

[13] USP<1220> Analytical Procedure Life Cycle. Coming into effect 01 May 2022.

MATERIAL REQUIREMENTS

Stability studies often require a significant amount of sample due to the inclusion of multiple analytical methodologies, multiple time points and multiple storage conditions.

For each storage condition, reserve samples should be included in the overall total number of samples placed in the stability chamber. This allows for the retesting of samples in case of unexpected events or results, as determined necessary and appropriate by an investigation. The number of reserve samples is often determined as an overall percentage of the number of samples placed on stability at each storage condition, or as a replicate of the number of samples required to be tested at each time point.

Further, per GMP guidelines, applicable to manufacturing of clinical trial product for use in the US[6] as well as in the European Union[14], it is required to withhold retains from each clinical batch manufactured. For both regions, it is recommended that twice the amount of material required for release testing be withheld. The retains should be appropriately stored for at least two years following clinical trial termination, or withdrawal of the clinical trial application.

CONCLUSION

Stability studies are challenging and require careful planning at an early development stage to support submission of a clinical trial application meeting regulatory expectations. Determining the best path forward and designing appropriate stability studies to support your application for FIH clinical trials is an essential part in ensuring success and receiving permission to proceed with the clinical study initiation. BDO's BioProcess Technology Group has the technical and regulatory expertise to help guide you in the design of stability studies that best support your product from a regulatory perspective.

[6] FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs. July 2008.

[14] EudraLex. The Rules Governing Medicinal Products in the European Union Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 13: Investigational Medicinal Products. 03 Feb 2010.

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CONTACT

LANCE MINOR
Principal, Life Sciences National Co-Leader
301-354-0711 / lminor@bdo.com

LOTTE MCNAMARA, P.H.D
Managing Director, BioProcess Technology Group
206-403-4029 / lmcnamara@bdo.com

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